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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/340,196	KATO ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59 and 68-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59 and 68-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/27/2005 has been entered.

2 The amendment filed 4/27/2005 is acknowledged. Claims 51, 53, 54 and 56 were canceled. Claim 78 was added. Claims 59 and 68-78 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections:

4. New claim 78 is objected to because it refers to using a "pectin" as a specific binding agent for differentiating between two different types of thyroglobulin. The specification contains no such teachings concerning "pectins". Therefore, it appears to be a typographical error. For examination purposes, claim 78 will be interpreted as directed to a method of using a lectin in the claimed method of determining malignancy of a thyroid tumor. Correction is required.

Claim Rejections Withdrawn:

5. The rejection of claims 59 and 68-78 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment and further in view of applicants' arguments pointing to support for clauses (iii) and (iv) in Figure 3, which is a summary of the data presented in Example 3.

Claim Rejections Maintained and New Grounds of Rejection:

6. Claims 59 and 68-78 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin". Additionally, with respect to claim 76, the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies" that are "reactive with an Lewis type sugar chain". With respect to claim 77, the clamed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies" that bind to a sugar chain with a specific structure found in thyroglobulin which is produced by a carcinoma cell.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants continues to assert that it is not necessary in general to provide working examples in order to

provide written description support for claimed matter. However, the basis for the rejection is that the structures of the antigens to which the antibodies bind have not been described. The specification cites Yamamoto (of record) as providing carbohydrate structures of thyroglobulin. However, Yamamoto provides "proposed" structures. Furthermore, the specification defines the phrase "capable of binding to a sugar chain structure" as having the meaning of "a lectin once bound to an affinity column can be eluted by this sugar". If this definition is applied to antibodies, then a sugar must be available to elute the antibody. The specification fails to provide such antibody/sugar pairs. A search of the prior art provides only one reference (Stanta, Thyroidology (1991) 3(1): 7-12) that teaches an antibody that binds to a particular type of thyroglobulin: thyroglobulin derived from "normal" thyroid tissue that is also bound by a concanavalin A-sepharose column (see page 9, 2nd full paragraph). However, the teaching of Stanta is not sufficient to show what sugar structure the antibody binds because Stanta teaches that the bound fraction derived from carcinomatous thyroid is not bound by this antibody (see Figure 6D; while both thyroglobulin species are bound by the lectin column, only the tyroglobulin from the "normal" thyroid tissue binds to the antibody of Stanta). Furthermore, Stanta appears to teach that this antibody was made fortuitously, and does not teach a repeatable method for making this antibody or for making other antibodies that may distinguish between thyroglobulin from malignant tissue and from non-malignant tissue. Because applicant has failed to demonstrate that it is well known in the art the sugar structures useful for making antibodies that would be useful in the claimed methods, this rejection is maintained. This is especially true for claims 76 and 77, where the antibody used in the claimed methods is one reactive with a Lewis type sugar chain or an antibody that would bind to a specific structure

found in thyroglobulin produced by a carcinoma cell. Applicant has previously indicated a contemplation of antibodies on page 6 of the specification in the interview of 14 July 2004, however, the specification fails to teach that any of the specific antibodies would be useful in distinguishing a first type of thyroglobulin from a second type of thyroglobulin or in specifically binding the a specific structure found in thyroglobulin produced by a carcinoma cell.

7. Claims 59, 68, 69, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nakamura (U.S. Patent 5,571,729; issued 11/5/1996) or Satomura (U.S. Patent 5,780,247; issued 7/14/1998; effective filing 1/5/1991) in view of either Yamamoto (of record), Tarutani (of record), Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only), or Stanta (Stanta, G. et al., Thyroidology, 3(1): 7-12, 1991).

The claimed inventions are drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amount of one of two types of thyroglobulin and also measuring the total amount of thyroglobulin. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin. All of the claimed inventions comprise the use of an anti thyroglobulin antibody that binds to both types of thyroglobulin. Claims 59, 69 and 74 comprise a separation step, where the lectin-thyroglobulin complex or sugar-specific antibody-thyroglobulin complex is separated prior to measuring the amount of the complex. Claims 59, 68 and 74 may comprise a step of directly measuring the amount of the second type of

thyroglobulin (that does not bind to the lectin or the sugar-specific antibody). Claims 59, 68, 69, and 74 comprise calculating a ratio of the amount of the first type of thyroglobulin to the total amount of thyroglobulin; or a ratio of the amount of the second type of thyroglobulin to the total amount of thyroglobulin. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Nakamura teaches a method for measuring two different types of glycoproteins (example is human chorionic gonadotropin (hCG) comprising adding to a sample containing the hCG an antibody that binds to both types of hCG and a lectin that selectively binds to only one of the two types of hCG. Nakamura teaches separation of the resulting complexes from each other by HPLC and teaches measuring the amounts of the two types in the sample (see col. 2, lines 23-40). Satomura teaches and claims methods for separating and simultaneously measuring the total of and specific components of analytes having similar structures, where the analytes have sugar chains, comprising mixing a sample with a first affinity substance that binds to all of the analytes in the sample and a second affinity substance that binds to at least one of the analytes but does not bind to at least one of the other analytes, where the second affinity substance may be a lectin and the first affinity substance may be an antibody (see claims 1, and 5-9). Thus, either Nakamura or Satomura teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest.

Neither Nakamura nor Satomura teaches methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and neither Nakamura nor Satomura

teaches a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor.

However, Yamamoto teaches that thyroglobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated from benign and from normal thyroids (page 138, first –2nd col.). Yamamoto teaches that the carbohydrate chains of thyroglobulin derived from the benign tumor had the same structures as those thyroglobulin derived from normal thyroid. Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid, contains less high-mannose type carbohydrate moieties, contains oligosaccharides of high molecular mass with repeating Gal-GlcNAc disaccharides and peripheral alpha-fucosyl residues than does thyroglobulin isolated from normal and benign thyroid tissue (page 142, 2nd col – page 143, 1st col). Yamamoto also teaches that using the lectin, ConA, one can differentiate between thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal and benign thyroid. ConA affinity chromatography demonstrates that thyroglobulin from malignant thyroids contains more triantenary complex-type oligosaccharides than thyroglobulin from normal thyroids; RCA affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Thus, Yamamoto provides teachings that allow one or ordinary skill in the art to predict that lectin affinity may be used as the basis for an assay to differentiate between thyroglobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin sample was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that either ConA-reactivity or RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Tarutani teaches that the percent of total thyroglobulin that binds to Con-A is different for trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue (see page 855, Table II). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin sample was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Tarutani teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Survilo teaches that thyroglobulin samples from cancerous thyroids did not bind as strongly to ConA-Sepharose as did those from normal or goiterous thyroids. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Survilo

teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids. Because either of Yamamoto, Tartani or Survilo teach that there is differential lectin reactivity between thyroglobulin from malignant and benign or normal thyroids, a different ratio of one type of glycoslated thyroglobulin to a second type of glycosylated thyroglobulin would be expected using the method of Katoh. Furthermore, Tarutani specifically demonstrates that for Con-A reactivity, there are different ratios of bound to unbound for thyroglobulin derived from normal versus cancerous thyroid samples in Table II on page 855.

Stanta teaches that thyroglobulin from a normal thyroid gland and from a well differentiated carcinoma were applied to a concanavilin A-sepharose column and for both types of thyroglobulin, two fractions were collected; one that that passed through the column unbound, and one that bound and was eluted after application of 0.5M methyl-alpha-glucoside. For thyroglobulin derived from thyroid carcinoma, the unbound fraction was larger than for thyroglobulin derived from the normal thyroid; and the bound (eluted fraction) was smaller than the bound fraction from normal fraction (see page 9, and Figure 5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin sample was derived from a patient with a malignant thyroid tumor or from a patient with either a benign or a normal thyroid, because Stanta teaches that ConA-reactivity distinguishes between thyroglobulin derived from a thyroid carcinoma and from a normal thyroid.

The prior art of record provides the motivation to use the general methods of Nakamura or Satomura using differential lectin reactivity for the purpose of distinguishing between differentially glycosylated glycoproteins (such as differentially glycosylated thyroglobulin) in combination with any of Yamamoto, Tarutani, Survilo or Stanta, because any of Yamamoto, Tarutani, Survilo or Stanta clearly teaches that thyroglobulin derived from a malignant thyroid has a differential pattern of lectin reactivity than does thyroglobulin derived from normal or benign thyroid.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that Yamamoto, Tarutani or Survilo fail to disclose measurement of total thyroglobulin specifically by using either an anti-thyroglobulin antibody, and also fails to specificallydiscloe any method for determining malignancy of thyroid tumors by using the calculated ratio recited in the claim. This argument is not found persuasive because Yamamoto, Tarutani, Survilo, newly found reference Stanta, clearly demonstrate a differential lectin-binding pattern between malignant and non-malignant thyroids. Because there is a different pattern of lectin-binding between thyroglobulin derived from malignant and non-malignant thyroids, a different ratio would necessarily be found for thyroglobulin derived from malignant compared to non-malignant thyroid. The methods of Nakamura or Satomura encompass the claimed methods. The teachings of Yamamoto, Tarutani, Survilo and Stanta demonstrate that thyroglobulin is an obvious species of glycoprotein encompassed by the methods of Nakamura or Satomura, because any of Yamamoto, Tarutani, Survilo or Stanta provides the teachings that malignant thyroids produce differently glycosylated thyroglobulin than does non-malignant thyroids, and further each of these references demonstrates this by showing differential lectin-binding.

8. Claims 70,71 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katoh (U.S. Patent 5,591,589; issued 1/7/1997) in view of either Yamamoto (of record), Tarutani (of record), Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only), or Stanta (Stanta, G. et al., Thyroidology, 3(1): 7-12, 1991).

Claims 70 and 71 are drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-thyroglobulin complex. Claim 71 comprises the use of an anti thyroglobulin antibody that binds to all types of thyroglobulin, regardless of whether the lectin is also bound. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign. Claim 78, although it uses the term "pectin", is interpreted to be drawn to methods using a "lectin", and it is assumed that "pectin" is a typographical error.

Katoh teaches and claims methods for separating and measuring two or more forms of glycoproteins that are different in sugar chain structure but have essentially the same protein structure, comprising mixing a sample with a lectin capable of recognizing the specific sugar chain structure of at least one of these glycoproteins to be measured, and a first antibody which has a property of bind to all the glycoproteins but does not bind to glycoproteins having the

lectin attached thereto; and separating and measuring glycoproteins having the first antibodies attached and glycoproteins having no first antibody attached. Additionally, Katoh teaches that a second antibody may be employed, where the second antibody binds to all of the glycoproteins regardless of whether the lectin is also bound (see claims 1, and 3). Thus, Katoh teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest.

Katoh fails to teach methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and Katoh fails to teach a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor.

However, Yamamoto teaches that thyroglobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated from benign and from normal thyroids (page 138, first –2nd col.). Yamamoto teaches that the carbohydrate chains of thyroglobulin derived from the benign tumor had the same structures as those thyroglobulin derived from normal thyroid. Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid, contains less high-mannose type carbohydrate moieties, contains oligosaccharides of high molecular mass with repeating Gal-GlcNAc disaccharides and peripheral alpha-fucosyl residues than does thyroglobulin isolated from normal and benign thyroid tissue (page 142, 2nd col – page 143, 1st col). Yamamoto also teaches that using the lectin, ConA, one can differentiate between thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal and benign thyroid. ConA affinity chromatography demonstrates that thyroglobulin from malignant thyroids contains more triantenary complex-type oligosaccharides than thyroglobulin from normal thyroids; RCA

affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Thus, Yamamoto provides teachings that allow one of ordinary skill in the art to predict that lectin affinity may be used as the basis for an assay to differentiate between thyroglobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that either ConA-reactivity or RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Tarutani teaches that the percent of total thyroglobulin that binds to Con-A is different for trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue (see page 855, Table II). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Tarutani teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Survilo teaches that thyroglobulin samples from cancerous thyroids did not bind as strongly to ConA-Sepharose as did those from normal or goiterous thyroids (an example of a benign condition). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Survilo teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Stanta teaches that thyroglobulin from a normal thyroid gland and from a well differentiated carcinoma were applied to a concanavilin A-sepharose column and for both types of thyroglobulin, two fractions were collected; one that that passed through the column unbound, and one that bound and was eluted after application of 0.5M methyl-alpha-glucoside. For thyroglobulin derived from thyroid carcinoma, the unbound fraction was larger than for thyroglobulin derived from the normal thyroid; and the bound (eluted fraction) was smaller than the bound fraction from normal fraction (see page 9, and Figure 5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin sample was derived from a patient with a malignant thyroid tumor or from a patient with either a benign or a normal thyroid, because Stanta teaches that ConA-reactivity distinguishes between thyroglobulin derived from a thyroid carcinoma and from a normal thyroid.

The prior art of record provides the motivation to use the general methods of Katoh using differential lectin-reactivity for the purpose of distinguishing between differentially glycosylated glycoproteins (such as differentially glycosylated thyroglobulin) in combination with any of Yamamoto, Tarutani, Survilo or Stanta, because any of Yamamoto, Tarutani, Survilo or Stanta clearly teaches that thyroglobulin derived from a malignant thyroid has a differential pattern of lectin-reactivity than does thyroglobulin derived from normal or benign thyroid.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants again assert that Yamamoto, Tarutani or Survilo fail to disclose measurement of total thyroglobulin specifically by using either an anti-thyroglobulin antibody, and also fails to specifically discloe any method for determining malignancy of thyroid tumors by using the calculated ratio recited in the claim. This argument is not found persuasive because Yamamoto, Tarutani, Survilo, and newly found reference Stanta, clearly demonstrate a differential lectin-binding pattern between malignant and non-malignant thyroids. Because there is a different pattern of lectin-binding between thyroglobulin derived from malignant and non-malignant thyroids, a different ratio would necessarily be found for thyroglobulin derived from malignant compared to non-malignant thyroid. The methods of Katoh encompass the claimed methods. The teachings of Yamamoto, Tarutani, Survilo and Stanta demonstrate that thyroglobulin is an obvious species of glycoprotein encompassed by the methods of Katoh, because any of Yamamoto, Tarutani, Survilo or Stanta provides the teachings that malignant thyroids produce differently glycosylated thyroglobulin than does non-malignant thyroids, and further each of these references demonstrates this by showing differential lectin-binding.

9. Claim 73 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Canfield (WO/87/00289;) in view of Yamamoto (of record).

The previous rejection is reiterated below:

Claim 73 is drawn to a method for determining malignancy of a thyroid tumor, where the methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin, where the sample is divided into two portions, with one portion one measures one of two types of thyroglobulin, and with the second portion, one measures total thyrogobulin levels. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-thyroglobulin complex. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Canfield teaches the use of differential lectin-reactivity as the basis for measuring desialated hCG levels (page 15). Canfield also teaches that this method may be used to measure differentially glycosylated thyroglobulin (page 9, lines 20-23). Canfield teaches a method for measuring desialated hCG as a percentage of total hCG in samples from patients having gestational trophoblastic tumors and from patients with a normal pregnancy (page 24, lines 19-24). In order to obtain the data for the ratios of desialated hCG to total hCG, Canfield provides an example where the data is obtained by at least two separate measurements that would have required separating the sample into at least two portions. Canfield teaches that asialated hCG

was measured in one instance with a RCA-^{125}I-R525 LIRMA and that total hCG was determined utilizing the B101-R525 IRMA (see page 24, lines 19-24). Therefore, Canfield teaches the method steps of the claimed methods, whereby a sample is divided into two portions.

While Canfield does teach that methods of using lectin-based assays may be used in combination with antibody assays to distinguish and quantitate desialated thyroglobulin from normally glycosylated thyroglobulin, Canfield fails to teach that measuring levels of desialated thyroglobulin is correlated of thyroid malignancy.

However, Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid than does the thyroglobulin of normal or benign thyroids, and that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Canfield in the measurement of differential lectin-reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Applicants argue that Canfield fails to suggest the determination of malignancy of thyoid tumor by using the amount of thyroglobulin having a specific structure of a sugar chain. This argument is not found persuasive. It appears that applicants have misconstrued the rejection of record. Canfield is cited to demonstrate that the methodology of using differential sialylation to

distinguish between two types of glycoprotein is known in the art, as is the method step of dividing a sample into two portions. The teachings of Yamamoto are the teachings that provide the motivation of one of skill in the art to combine the general teachings of Canfield with Yamamoto, because Yamamoto teaches that thyroglobulin from malignant thyroid tumor contains less sialic acid than does thyroglobulin from normal or benign thyroids, and further because Yamamoto teaches that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains (i.e. less sialylation of carbohydrate chains) than does thyroglobulin from normal thyroids. Therefore, the association between malignancy in thyroid disease and degree of sialylation of carbohydrate chains is established by the prior art and one would therefore be motivated to use the method of Canfield to measure this and state this in terms of ratios.

10. Claim 75 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Katoh (supra) in view of Canfield (WO/87/00289;) and further in view of Yamamoto (supra) for the reasons of record.

The previous rejection is reiterated below:

Claim 75 is drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin. The claimed invention comprises the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-

thyroglobulin complex. The claimed methods comprise the measurement of total amount of thyroglobulin, whereby the sample is divided into two portions, with one portion one measures one of two types of thyroglobulin, and with the second portion, one measures total thyrogobulin levels. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Katoh teaches and claims methods for separating and measuring two or more forms of glycoproteins that are different in sugar chain structure but have essentially the same protein structure, comprising mixing a sample with a lectin capable of recognizing the specific sugar chain structure of at least one of these glycoproteins to be measured, and a first antibody which has a property of binding to all the glycoproteins but does not bind to glycproteins having the lectin attached thereto; and separating and measuring glycoproteins having the first antibodies attached and glycoproteins having no first antibody attached. Thus, Katoh teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity.

Katoh fails to teach methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and Katoh fails to teach a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor. Additionally, although Katoh teaches that one may measure total amounts of the glycoprotein of interest, Katoh fails to teach that this step may be done by first dividing a sample into two portions, where one of the portions is used to measure total amount of glycoprotein.

However, Canfield teaches the use of differential lectin-reactivity as the basis for measuring desialated hCG levels (page 15). Canfield also teaches that this method may be used

to measure differentially glycosylated thyroglobulin (page 9, lines 20-23). Canfield teaches a method for measuring desialated hCG as a percentage of total hCG in samples from patients having gestational trophblastic tumors and from patients with a normal pregnancy (page 24, lines 19-24). In order to obtain the data for the ratios of desialated hCG to total hCG, Canfield provides an example where the data is obtained by at least two separate measurements that would have required separating the sample into at least two portions. Canfield teaches that asialated hCG was measured in one instance with a RCA-^{125}I-R525 LIRMA and that total hCG was determined utilizing the B101-R525 IRMA (see page 24, lines 19-24). Therefore, Canfield teaches the method steps of the claimed methods. The teachings of Katoh in combination with those of Canfield provide methods where differentially glycosylated thyroglobulin may be measured as a percent of total thyroglobulin.

While Canfield does teach that methods of using lectin-based assays may be used in combination with antibody assays to distinguish and quantitate desialated thyroglobulin from normally glycosylated thyroglobulin, Canfield fails to teach that measuring levels of desialated thyroglobulin is correlated of thyroid malignancy.

However, Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid than does the thyroglobulin of normal or benign thyroids, and that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in combination with Canfield in

the measurement of differential lectin reactivity to determine if a sample of thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that the combination of references does not provide the measurement of thymoglobulin specifically by using either an anti-thyrolobulin antibody, or to disclose any method for determining malignancy of thyroid tumor by using the calculated ratio recited in the claims. This is not found persuasive, because Katoh clearly teaches the use of an anti-glycoprotein antibody that would encompass an anti-thyroglobulin antibody. Furthermore, Yamamoto clearly teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid than does the thyroglobulin of normal or benign thyroids, and that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Therefore, one would be motivated to use the general method of Katoh in the specific case of determining different sialylation pattern of thyroglobulin for the purpose of differentiating a sample of thyroglobulin from a malignant thyroid as opposed to a non-malignant thyroid, because Yamamoto provides the data demonstrating that a ratio of the differentially RCA-bound thyrogloublins would be necessarily different (because of differences in degree of sialylation). Canfield is cited to provide the step of dividing a sample into two portions, and demonstrates that such a method step is known in the prior art.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 59, 68, 69, and 74 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 5-9 of U.S. Patent No. 5,780,247 in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). The claimed inventions are an obvious species of method that are within the scope of claims 1 and 5-9 of U.S. Patent No. 5,780,247. In view of the teachings of either Yamamoto, Tarutani or Survilo, that thyroglobulin is a glycosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern, and in view of the teachings that this can be observed by measuring differences in lectin-reactivity, the claimed inventions are an obvious species of the methods of claims 1 and 5-9 or U.S. Patent 5,780,247.

Applicants' arguments are unpersuasive for the reasons set forth above in the response to the arguments against the rejections under 103(a) over the cited references.

14. Claims 70, 71 and 78 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,591,589 in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). The claimed inventions are an obvious species of method that are within the scope of claims 1 and 3 of U.S. Patent No. 5,591,589. In view of the teachings of either Yamamoto, Tarutani or Survilo, that thyroglobulin is a glycosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern, and in view of the teachings that this can be observed by measuring differences in lectin-reactivity, the claimed inventions are an obvious species of the methods of claims 1 and 3 or U.S. Patent 5,591,589.

Applicants' arguments are unpersuasive for the reasons set forth above in the response to the arguments against the rejections under 103(a) over the cited references.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
July 25, 2005

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PRIMARY EXAMINER